Complete Summary

GUIDELINE TITLE

Use of dexrazoxane as a cardioprotectant in patients receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer.

BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Seymour L, Bramwell V. Use of dexrazoxane as a cardioprotectant in patients receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jan. 23 p. (Practice guideline report; no. 12-5). [24 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Anthracycline-related cardiac toxicity
- Non-hematologic malignancies

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate if dexrazoxane should be used routinely in patients with advanced or metastatic cancer who are at risk of developing cardiotoxicity when receiving chemotherapy containing doxorubicin or epirubicin
- To evaluate if the available data support the use of dexrazoxane in the adjuvant setting for patients at risk of developing cardiotoxicity

TARGET POPULATION

Adult patients with nonhematologic malignancies receiving anthracycline-containing chemotherapy

INTERVENTIONS AND PRACTICES CONSIDERED

Use of dexrazoxane as a cardioprotectant in patients who are receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer

MAJOR OUTCOMES CONSIDERED

- Clinical and subclinical cardiotoxicity
- Noncardiac toxicity
- Impact on efficacy outcomes such as response and overall survival

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original 1998 Guideline

MEDLINE and CANCERLIT searches were performed for the years 1987 to November 1997. The search terms included the following medical subject headings (MeSH): dexrazoxane, neoplasms, practice guidelines, meta-analysis, randomized controlled trials, double-blind and single-blind method; and the following text words: dexrazoxane, randomized controlled trial, and random. The search also included the following publication types: practice guideline, meta-analysis, and randomized controlled trial. This search was updated in March 1998. The Physician Data Query (PDQ) clinical trials database and the 1995, 1996, and 1997 American Society for Clinical Oncology (ASCO) proceedings were searched for reports of new or on-going trials. Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were searched for additional trials.

January 2004 Update

The original literature search has been updated using MEDLINE (through January 2004), EMBASE (through January 2004), the Cochrane Library (Issue 4, 2003), and the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO), 1998–2003.

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were or included:

1. Randomized controlled trials comparing dexrazoxane with a placebo or no treatment
2. Patients receiving chemotherapy containing doxorubicin or epirubicin
3. Trials reporting on clinical or subclinical cardiotoxicity, noncardiac toxicity, response rates, or overall survival
4. Patients with nonhematologic malignancies
5. Abstracts of trials were also considered.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.

NUMBER OF SOURCE DOCUMENTS

Original 1998 Guideline

Seven randomized controlled trials were identified, six trials reported fully in the published literature, and one trial reported only in abstract form.

January 2004 Update

One evidence-based practice guideline developed in 1999 and updated in 2002 was identified and added in June 2002. No new evidence was located in the most recent review of the literature (January 2004).

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Original 1998 Guideline

Synthesizing the Evidence: Combining results across trials provided added power to detect the efficacy of a treatment and increased the precision of the estimate. The outcome measures used to report clinical and subclinical cardiotoxicity were consistent from trial to trial (congestive heart failure [CHF], a decrease in left ventricular ejection fraction [LVEF] $\geq$20% from baseline, and a fall in resting left ventricular ejection fraction to $\leq$45%), but in some cases these data were reported together. Since the data for clinical cardiotoxicity were reported separately for all but one trial, it was decided to pool the results for this outcome measure to obtain a more precise estimate of the treatment effect of dexrazoxane. Tests of heterogeneity were conducted to assess whether the differences in chemotherapy regimen (doxorubicin or epirubicin), dose ratio of dexrazoxane to chemotherapy agent, or tumour type contributed to the effect. Since there was a question about the contribution of dexrazoxane to the antitumour effect of the chemotherapy agent, the objective response results were also pooled.

The results were pooled using the software package, Metaanalyst [0.988], provided by Dr. Joseph Lau of Boston, MA.

Due to suspected statistical heterogeneity across studies related to differences in methodological quality, dose ratio, chemotherapy regimen, and tumour type, a random effects model was used for the meta-analysis.

January 2004 Update

The information pertaining to the 1998 guideline, listed above, remains current.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Systemic Treatment Disease Site Group (DSG) noted that most trials of dexrazoxane were conducted in patients with advanced breast cancer, and discussed the use of dexrazoxane in tumour sites other than the breast. There were two trials that demonstrated an effect on cardiotoxicity in patients with other tumour sites that was consistent with that in breast cancer patients. It was decided to recommend dexrazoxane for use in tumour sites other than advanced breast cancer, with a statement that further research should be undertaken to assess the effects in other tumour sites.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Original 1998 Guideline

One article was identified that reports the results of an economic assessment of dexrazoxane in patients with stage IIIB or IV carcinoma of the breast receiving 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC). This economic analysis is a modelling study, based on the patients in the two trials reported by Swain et al described in the original guideline document. The patients received six cycles of 5-fluorouracil, doxorubicin, and cyclophosphamide without dexrazoxane at which point they received open-label dexrazoxane. It should be noted again that the reporting of these trials is flawed, with a number of patients omitted from the analyses. In addition, this analysis is based on modelling, rather than on actual data collected during the study. Therefore, the results should be considered with caution.

Two cost-effectiveness analyses were done. In the first analysis, the cost of each cardiac event prevented was calculated over a one-year period. The model included costs of tests and procedures associated with chemotherapy and cardiac events (congestive heart failure [CHF] and declines in left ventricular ejection fraction [LVEF]) as well as the cost of dexrazoxane. The analysis resulted in a cost of Can$5,745 for each cardiac event prevented by using dexrazoxane. In addition, the cost of preventing one congestive heart failure event was calculated to be Can$13,182. A second cost-effectiveness study was done, but the assumptions used in the model were so extreme that the information was not credible to the guideline developers.

Dexrazoxane is sold in Canada at approximately $0.50/mg, or $250 per 500 mg vial. Based on a dosage ration of 10:1 (dexrazoxane:doxorubicin) and assuming it is given once per cycle, the cost of dexrazoxane would be $250 per cycle.

January 2004 Update

There is no additional evidence on this topic at this time.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 168 practitioners in Ontario (130 medical oncologists, 34 pharmacists, two radiation oncologists, and two hematologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks

(post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Systemic Treatment Disease Site Group (DSG).

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- The evidence supports the use of dexrazoxane to protect against the cardiotoxicity associated with conventional-dose doxorubicin in patients with advanced but anthracycline-sensitive cancer, in whom the continued use of anthracycline-containing chemotherapy is indicated in the opinion of the treating physician, and who have received 300 mg/m^2 or more of doxorubicin.
- The evidence supports the use of dexrazoxane to protect against the cardiotoxicity associated with conventional-dose epirubicin in patients with advanced but anthracycline-sensitive cancer, in whom the continued use of anthracycline-containing chemotherapy is indicated in the opinion of the treating physician. There are no data indicating the optimal cumulative dose of epirubicin at which dexrazoxane should be instituted. For doxorubicin, use of dexrazoxane is recommended after the cumulative dose reaches 300 mg/m^2 (i.e., 55% of the recommended maximum). A similar formula could be used for epirubicin; that is, institution of dexrazoxane when the cumulative dose of epirubicin reaches 550 mg/m^2, as the recommended maximum cumulative dose in Canada is 1,000 mg/m^2.
- Preclinical studies did not show any cardioprotectant effect for dexrazoxane when used with mitoxantrone, and no clinical studies have been done. Therefore, dexrazoxane is not recommended for use with mitoxantrone.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and a meta-analysis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Seven randomized controlled trials (RCTs), two with placebo control, were reviewed. Clinical cardiotoxicity data from six trials were pooled (n = 1,070). The meta-analysis indicated that the risk of experiencing clinical cardiotoxicity was significantly reduced by dexrazoxane (odds ratio 0.21; 95% confidence

interval [CI], 0.08 to 0.51; p = 0.0006). There was no significant benefit shown in individual trials for objective response or survival.
- One of the randomized controlled trials revealed a significantly lower objective response rate in the dexrazoxane arm. However, a meta-analysis of objective response across five trials of breast cancer patients (n = 818) did not confirm this effect (odds ratio, 0.80; 95% confidence interval, 0.61 to 1.06; p = 0.12).

POTENTIAL HARMS

- The use of dexrazoxane increased the incidence of myelosuppression and other noncardiac toxicities, but these were generally mild.
- Noncardiac toxicities were reported in the studies. There were trends noted toward increased hematologic toxicity for chemotherapy plus dexrazoxane compared with chemotherapy alone, including the incidence of thrombocytopenia, lower platelet and white blood cell nadirs, and greater median time to recovery of an absolute neutrophil count (ANC) 1,000 mL (see Table 4 of the original guideline document for detailed results). Other toxicities associated with dexrazoxane were pain at the injection site, stomatitis, and phlebitis.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- There is no evidence to support or refute the use of dexrazoxane in the adjuvant setting for any tumour type. Because of concerns that dexrazoxane may reduce the efficacy of anthracyclines, and because data are not yet available on long-term toxicities, further studies should be performed before the drug is used in this setting.
- The majority of published studies of dexrazoxane have been performed on patients with breast cancer. Two trials in patients with other tumour sites (small-cell lung cancer and pediatric sarcoma) report beneficial effects on cardiotoxicity consistent with those for breast cancer. These results lend support to the use of the drug in conjunction with doxorubicin in patients with other tumour sites, although further studies should be performed to confirm these benefits. There are no data on the use of dexrazoxane in patients with hematologic malignancies.
- There are no data on the use of dexrazoxane in patients with preexisting cardiac disease or anthracycline-induced cardiotoxicity; further studies should be performed in these settings.
- There are no data available regarding interaction between dexrazoxane and chemotherapeutic agents other than doxorubicin, epirubicin, cyclophosphamide, 5-fluorouracil, or vincristine, and care should be exercised before using dexrazoxane with regimens that contain drugs other than these.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Seymour L, Bramwell V. Use of dexrazoxane as a cardioprotectant in patients receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jan. 23 p. (Practice guideline report; no. 12-5). [24 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 November 16 (revised online 2004 Jan)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Systemic Treatment Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Systemic Treatment Disease Site Group (DSG) disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The guideline developer instituted a new format for their guidelines and evidence summaries: A SUMMARY of the original Practice Guideline or Evidence Summary, integrated with the most current information, replaces the ABSTRACT, RECOMMENDATION, BRIEF REPORT and EVIDENCE UPDATE.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of dexrazoxane as a cardioprotectant in patients receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer. Summary. Toronto (ON): Cancer Care Ontario, 1998 Nov 16 (updated online 2004 Jan). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This NGC summary was updated by ECRI on December 14, 2001. The update information was verified by the guideline developer as of January 10, 2002. This summary was updated again on October 29, 2002. The information was verified by the guideline developer on November 15, 2002. This summary was updated again on June 29, 2004. The information was verified by the guideline developer on July 19, 2004.

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